

# Trends and disparities in the use of cholinesterase inhibitors to treat Alzheimer's disease dispensed by the Brazilian public health system – 2008 to 2014: a nation-wide analysis

Tendência e desigualdade no uso de anticolinesterásicos para tratamento de doença de Alzheimer dispensados pelo sistema de saúde público do Brasil – 2008 e 2014: uma análise nacional

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## ABSTRACT

In light of the high cost of dementia treatment, there is legislation authorizing free distribution of cholinesterase inhibitors to those suffering from Alzheimer's disease in Brazil. However, the existence of this free distribution does not guarantee adequate distribution. **Objectives:** The present study aimed to investigate the trends of prescriptions and the coverage of Alzheimer's disease treatment using cholinesterase inhibitors from public pharmacies dispensing high-cost drugs in Brazil. **Methods:** This was a retrospective study that collected data from the Brazilian public Unified Health System. All cholinesterase inhibitors distributed at no cost to Brazilians during the year 2014, as well as the estimated number and percentages of patients who used these medications, were evaluated and compared to data from the year 2008. **Results:** Our estimates indicated that 9.7% of the population having dementia syndromes used cholinesterase inhibitors, as well as 16.1% of those with Alzheimer's disease in Brazil. A clear disparity was noted between the use and distribution of cholinesterase inhibitors, depending on the region in which they were found. Over time, an increase in the distribution of cholinesterase inhibitors has been noted. In 2008, that use was 12.0% whereas, in 2014, it was 16.1%, an increase of 34% in six years. **Conclusion:** It was estimated that 16.1% of patients with Alzheimer's disease in Brazil use cholinesterase inhibitors. These values have increased and, in spite of not being satisfactory, they indicate a potential for improvement. However, there is still a significant disparity among the regions.

**Keywords:** cholinesterase inhibitors; public health; dementia; Alzheimer's disease

## RESUMO

Devido ao custo alto de tratamento, existe uma legislação autorizando a distribuição sem custo de anticolinesterásicos para pacientes com doença de Alzheimer no Brasil. Entretanto, a existência dessa distribuição gratuita nem sempre garante uma distribuição adequada. **Objetivos:** O presente estudo objetiva investigar a distribuição e desigualdades no uso de anticolinesterásicos (AChE) dispensados pelo Sistema de Saúde Público do Brasil. **Métodos:** Estudo retrospectivo que coletou dados do Sistema Único de Saúde brasileiro. Foram avaliados todos os anticolinesterásicos distribuídos sem custo no Brasil durante o ano de 2014, assim como o número estimado e a porcentagem de pacientes que usavam essa medicação. Esses dados foram comparados com o ano de 2008. **Resultados:** Estima-se que 9,7% da população que possui síndromes demenciais usa anticolinesterásicos, assim como 16,1% dos pacientes com doença de Alzheimer. Uma clara desigualdade entre o uso e a distribuição dos anticolinesterásicos foi encontrada, variando de acordo com a região. Houve um aumento na distribuição de anticolinesterásicos ao longo do tempo. Em 2008, o uso era de 12% e, em 2014, foi de 16,1%, resultando em um aumento de 34% em 6 anos. **Conclusão:** Estima-se que 16,1% dos pacientes com doença de Alzheimer no Brasil usam anticolinesterásicos. Esses valores tiveram um aumento e, embora ainda não sejam satisfatórios, eles indicam um potencial de melhora. Entretanto, ainda foi evidenciada uma significativa desigualdade entre as regiões.

**Palavras-chave:** Inibidores da colinesterase; saúde pública; demência; Doença de Alzheimer

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The aging population is a global process that is altering the characterization of modern society, and Brazil is considered one of the developing countries with the highest rates of demographic aging<sup>1</sup>. This rapid Brazilian demographic transition brings with it new demands on public health services, which need to direct measures and resources to the treatment of older persons. Among health problems occurring more frequently in this phase of life, neurodegenerative diseases, including dementia syndromes, have a high prevalence, affecting approximately 8.5% of older people in Latin America<sup>2</sup>.

Alzheimer's disease (AD) is the main cause of irreversible dementia in older Brazilians<sup>3</sup>, and is characterized by neuron loss that leads to cognitive (memory, orientation, language, and attention) deficits as well as functional, social, and occupational impairments. In spite of AD's physiopathology not being totally known, studies indicate that alterations in the concentration of acetylcholine are responsible for part of the disease's symptoms<sup>4</sup>. Based on the possible cholinergic deficit and aiming to increase that substance's synaptic availability, cholinesterase inhibitors are the principal drugs currently used for the specific treatment of this disease. They also act by inhibiting catalytic enzymes such as, acetyl- and butyrylcholinesterase. This therapy is aimed at improving patients' quality of life and keeping them independent longer in their activities of daily living<sup>5</sup>.

The cholinesterase inhibitors approved for use in Brazil are rivastigmine, donepezil and galantamine. The estimated annual cost of treatment for persons with AD varies from US\$868 in very low income regions to US\$32,865 in high income regions per person<sup>6</sup>. In light of this treatment's high cost, there is legislation authorizing free distribution of cholinesterase inhibitors to those suffering from mild to moderate AD in Brazil, according to the authority established in Article 5 of the Decree GM/MS no. 1230, from October 14, 1999, which includes the list of medications for AD in the Ambulatory Information System of Brazil's Unified Health System for medications that should be distributed.

The distribution of medication for treating AD is based on the evidence-based Brazilian public guidelines<sup>7</sup>, used by Brazil's Ministry of Health since 2002. In addition to the pharmaceuticals already cited, there are other therapeutic possibilities that include transdermal rivastigmine and orally-administered memantine<sup>8</sup>. They, however, were not freely distributed until the end of 2017. The absence of these two medications in the Brazilian public guidelines had resulted in judicial demands that they be distributed, increasing costs for the Unified Health System (SUS) in its diverse governmental entities.

In spite of being well structured, the existence of the Brazilian public guidelines does not guarantee the measure's total effectiveness. Difficulties are encountered in adequate distribution, like accessibility and availability proportional to the number of cases in each municipality<sup>9</sup>. Prioritizing

adequate distribution of drugs indicated for treatment of AD, in light of its importance to both patients and the national public health system, makes it necessary to evaluate whether or not there is a convenient association between the estimated number of those suffering from the disease and the distribution of high-cost medications throughout the country's federative units.

This study's objective was to investigate the trends of prescription (in 2008 and 2014) and the coverage of AD treatment using cholinesterase inhibitors from pharmacies dispensing high-cost drugs in Brazil, evaluating the types of medication most often used and the regions that dispense the most medications. We also compared the different regions in relation to coverage of treatment for dementia in general and for AD.

## METHODS

This was a retrospective study collecting data from the Brazilian public Unified Health System. This data collection did not need approval by an ethics committee as it dealt with governmental databanks for public access and use, according to Brazil's National Council of Health Resolution CNS 466/12.

The study was conducted for the year 2015, extracting data on the use of cholinesterase inhibitors contained in the Information Technology Department of the Unified Health System's (DATASUS's) "Health Information (TABNET)". In order to extract the data, DATASUS was accessed using the link <http://www2.datasus.gov.br/DATASUS/index.php?area=02>. In "Health Services", "Ambulatory Production" was chosen and in "Procedure", categories related to cholinesterase inhibitors were selected (for example: 0601220030: rivastigmine (N) 1.5 MG - BY CAPSULE). Once the cholinesterase inhibitor was selected, the quantity approved for each municipality in each state was consulted. This data was exported to Excel tables for later compilation.

To extract the number of older people in Brazil and its states, the Brazilian Institute of Geography and Statistics site was used, following the link <http://www.ibge.gov.br/apps/snig/v1/?loc=0,P12,P27&cat=-1,-2,8,128&ind=4711> and also exported to an Excel table.

In order to facilitate the comparison of data with a previous study using the same method of collection, we opted to use a prevalence of dementia of 7.1% in Brazil and, of the patients with dementia, it was estimated that 60% had AD<sup>10</sup>.

Thus, 20,589,903 older people were counted by the Brazilian Institute of Geography and Statistics for the year 2010 (the year in which the demographic census was conducted). We then estimated that 1,461,812 were suffering from dementia and 877,087 from AD. The number of patients who used cholinesterase inhibitors was calculated by dividing the number of pills dispensed by one year (365 days). In other words, we considered that each patient would

use one cholinesterase inhibitor pill per day, which is the correct dosage in the case of galantamine and donepezil. That, however, overestimates the use of rivastigmine, which calls for a maximum dosage of two per day. We opted not to include rivastigmine oral solution 2mg/ml in the study as it is the only formula using drops, and it was observed that its values were not statistically significant (corresponding to less than 0.2% of medications dispensed) during our initial analysis. At that time, transdermal rivastigmine and memantine were not provided free of cost by the Brazilian public health system.

Once we had determined the number of patients who used cholinesterase inhibitors, we estimated the percentage of patients with dementia and with AD in both Brazil, and each state, being treated for their condition (coverage of the use of cholinesterase inhibitors).

Finally, the goal of furnishing cholinesterase inhibitor drugs to at least 50% of Alzheimer's patients was used. This goal was based on a previous study<sup>10</sup> and was guided by the premise that half of the patients had advanced stage AD, intolerance to cholinesterase inhibitors and/or criteria for exclusion from using the medication, as established in Decree 843, of the Brazilian Clinical Protocol and Therapeutics Directives for Alzheimer's Disease.

## RESULTS

In the year 2014, a total of 39,431,562 doses of cholinesterase inhibitors were distributed by pharmacies dispensing high-cost drugs in Brazil. Of these, 47.2% were rivastigmine, 36.3% were donepezil, and 16.5% galantamine. The most frequently dispensed was donepezil 10 mg (22.7%), followed by rivastigmine 3 mg (15%) and rivastigmine 6 mg (14.3%). The Southeast region dispensed the higher number of drugs (69.3%), followed by the South (13.5%) and the Northeast (12.5%). São Paulo was the state with the greatest rate of distribution (52.9%), followed by Minas Gerais (8.7%), and Paraná (8.4%). The description of the most-frequently used dosages of cholinesterase inhibitor can be found in Table 1.

Table 2 shows the estimated percentage of patients using cholinesterase inhibitors. Considering the use of one cholinesterase inhibitor pill per day, we found that 9.7% of the population with dementia syndromes, and 16.1% of those with AD, used that medication.

In separating out the states, we took note of the clear disparity among both the use and distribution of cholinesterase inhibitors, depending on the region in which they were found. Considering the use for dementia in general, the region with the highest estimated usage of cholinesterase inhibitors was the Southeast (11.1%), followed by the South (6.2%), the Central-West (4.5%), the Northeast (3.5%), and the North (1.6%). As for the states, Espírito Santo had the highest percentage of use (18.5%), followed by São

Paulo (16.9%), and Paraná (10.9%). Considering use for AD, the region with the highest estimated use of cholinesterase inhibitors was the Southeast (18.4%), followed by the South (10.4%), the Central-West (7.5%), Northeast (5.8%), and the North (2.6%). Of the states, Espírito Santo had the highest percentage of use (30.9%), followed by São Paulo (28.1%) and Paraná (18.2%).

Table 3 shows the comparison between the data extracted for 2008, published by Moraes et al.<sup>10</sup> and the data extracted for 2014, published in this study. An increase in the use of cholinesterase inhibitors dispensed in pharmacies distributing high-cost drugs was noted. In 2008, that usage was 12.0%, while in 2014 it was 16.1%, an increase of 34% in six years. In spite of some states having had an important increase (São Paulo, Espírito Santo, Mato Grosso do Sul, and Paraná), other states showed a decrease in medications distributed (Minas Gerais, Piauí, Rio Grande do Norte, and Sergipe).

If we consider the Brazilian government's goal of 50% of AD patients being treated, we note that there was a growth from 24% to 32.2% of the goal, with some states such as Espírito Santo (61.8%) and São Paulo (56.2%) being closer to the goal than others.

## DISCUSSION

This study has shown that, despite still being far below the goal of 50%, there has been an increase in dispensing cholinesterase inhibitor drugs in Brazil in recent years. In spite of this increase, there still is significant heterogeneity among the country's regions, with some states being near the goal and others still very distant.

In the year 2014, Brazil reached a 16.1% distribution of cholinesterase inhibitor drugs furnished by the Brazilian public Unified Health System, an increase when compared to the numbers for 2008, in which distribution was 12%. In a multicenter European study, the authors found that the prevalence of cholinesterase inhibitor use for patients with dementia was 10.3%, with a variation from 3.0% for Holland to 20.3% for France<sup>11</sup>. Despite these results being similar to those found in our study, where we found a prevalence of 9.7% for all of Brazil (varying from 0.3% in Amapá to 16.9% in São Paulo), the European study was conducted in 2004, which leads to the expectation that these numbers may have been much higher in 2014, when our study was conducted. The under-treatment rates observed by this and also by international studies may be directly related to the under-diagnosis of this condition worldwide, showing the need for global awareness and training for the identification of AD and other dementia syndromes.

Another fact to be highlighted is the nearly 35% growth in the use of cholinesterase inhibitors in Brazil in six years (2008 to 2014). This pattern of increased treatment is also

Table 1. Dosages (number of pills) of the most frequently-used anticholinesterases dispensed in 2014 in Brazil and its states.

State	Donepezil		Galantamine	Galantamine	Galantamine	Rivastigmine	Rivastigmine	Rivastigmine	Rivastigmine	Total	%
	5 mg	10 mg	8 mg	16 mg	24 mg	1.5 mg	3 mg	4.5 mg	6 mg		
Southeast											
São Paulo	2938635	4664107	1128086	944308	2068403	2191580	2812223	1338400	2765636	27317389	69.3
Rio de Janeiro	121719	238589	35830	61708	63573	119278	202495	150767	307768	20851378	52.9
Minas Gerais	636620	1266707	112497	210561	321282	120	120	247025	617115	1301727	3.3
Espírito Santo	248036	308075	65964	0	97066	270404	568260	187218	7214	3412047	8.7
Northeast											
Alagoas	18033	36014	2173	5453	12841	12295	16050	13410	44958	1752237	4.4
Bahia	89325	143109	10609	9262	13583	82807	141042	70943	171909	4922040	12.5
Ceará	164045	254808	32771	69697	64215	61986	121279	124182	192398	161227	0.4
Maranhão	48207	50461	44535	31317	7450	77846	121150	53512	120	732589	1.9
Paraíba	99557	104647	33431	63645	30293	165289	198768	98824	71702	1085381	2.8
Pernambuco	51183	119603	14499	14146	77446	30294	30346	90047	180346	434598	1.1
Piauí	45540	102837	5952	18052	18848	24976	31770	22320	62100	866156	2.2
Rio Grande do Norte	58202	136752	7072	12545	16612	30173	67566	51888	99622	607910	1.5
Sergipe	31890	53223	1770	9090	14557	16080	49740	20160	24842	332395	0.8
Central-west											
Distrito Federal	8520	21862	6051	0	6375	3390	6540	9480	22230	480432	1.2
Goiás	50386	119119	31228	33286	67803	54120	92520	54032	141756	221352	0.6
Mato Grosso	11068	49111	3738	4003	7149	15224	40858	11314	22672	1436173	3.6
Mato Grosso do Sul	49800	54231	27901	30330	9812	91830	133980	68944	75510	84448	0.2
North											
Acre	2078	330	270	240	240	11632	15300	2070	1080	644250	1.6
Amapá	90	382	0	0	0	360	1372	0	480	165137	0.4
Amazonas	22163	22909	2760	9276	15670	19410	54812	0	0	542338	1.4
Pará	40545	28904	6861	3200	9219	5858	8850	7800	19531	443986	1.1
Rondônia	15840	1950	420	390	0	0	25860	1080	360	33240	0.1
Roraima	2153	565	0	0	0	6180	10881	542	0	147000	0.4
Tocantins	90	3556	126	0	361	14400	24810	10050	10680	130768	0.3
South											
Paraná	254507	841290	96659	128603	175428	416640	605111	270358	529779	45900	0.1
Rio Grande do Sul	35011	94737	8514	10420	7658	46167	56084	23686	37598	20321	0.1
Santa Catarina	299201	244406	28128	30041	26168	259211	482473	104396	199700	64073	0.2
Total	5342444	8962284	1707845	1699573	3132052	4027550	5920260	3032448	5607106	5311974	13.5
%	13.6	22.7	4.3	4.3	7.9	10.2	15.0	7.7	14.3	3318375	8.4
	36.3			16.5						319875	0.8
										1673724	4.2
										39431562	100.0
										100.0	
							47.2				

**Table 2.** The use of anticholinesterases from pharmacies dispensing high-cost drugs in the year 2014 in Brazil and its Regions/States.

Region/State	Total of pills	Total estimate of patients using cholinesterase inhibitors	Total estimate of patients with dementia	% treated dementia with cholinesterase inhibitors	Estimate of patients with Alzheimer	% treated Alzheimer with cholinesterase inhibitors
Southeast	27317389	74842	676437	11.1%	405862	18.4
São Paulo	20851378	57127	338799	16.9%	203280	28.1
Rio de Janeiro	1301727	3566	147645	2.4%	88587	4.0
Minas Gerais	3412047	9348	164087	5.7%	98452	9.5
Espírito Santo	1752237	4801	25905	18.5%	15543	30.9
Northeast	4922040	13485	387101	3.5%	232261	5.8
Alagoas	161227	442	19608	2.3%	11765	3.8
Bahia	732589	2007	102951	1.9%	61770	3.2
Ceará	1085381	2974	64554	4.6%	38733	7.7
Maranhão	434598	1191	40304	3.0%	24182	4.9
Paraíba	866156	2373	32028	7.4%	19217	12.3
Pernambuco	607910	1666	66510	2.5%	39906	4.2
Piauí	332395	911	23556	3.9%	14133	6.4
Rio Grande do Norte	480432	1316	24384	5.4%	14631	9.0
Sergipe	221352	606	13206	4.6%	7924	7.7
Central West	1436173	3935	87932	4.5%	52759	7.5
Distrito Federal	84448	231	14059	1.6%	8435	2.7
Goiás	644250	1765	39792	4.4%	23875	7.4
Mato Grosso	165137	452	17070	2.7%	10242	4.4
Mato Grosso do Sul	542338	1486	17011	8.7%	10207	14.6
North	443986	1216	76770	1.6%	46062	2.6
Acre	33240	91	3323	2.7%	1994	4.6
Amapá	2684	7	2466	0.3%	1480	0.5
Amazonas	147000	403	14922	2.7%	8953	4.5
Pará	130768	358	37947	0.9%	22768	1.6
Rondônia	45900	126	8006	1.6%	4804	2.6
Roraima	20321	56	1759	3.2%	1056	5.3
Tocantins	64073	176	8346	2.1%	5007	3.5
South	5311974	14553	233573	6.2%	140144	10.4
Paraná	3318375	9091	83223	10.9%	49934	18.2
Rio Grande do Sul	319875	876	103765	0.8%	62259	1.4
Santa Catarina	1673724	4586	46586	9.8%	27951	16.4
Total	39431562	141221	1461812	9.7%	877087	16.1

confirmed by other studies. In Germany, for example, the standardized prevalence of cholinesterase inhibitors for people aged 65 or older, doubled in a period of eight years (2000 to 2007)<sup>12</sup> and in Italy, there was an increase of 40% in the prescription of these medications from 2002 to 2007<sup>13</sup>. However, a recent study carried out in France showed an increase in prescription rates between 2006 and 2010 and a decrease in prescription rates from 2011 to 2014<sup>14</sup>.

In regard to the types of cholinesterase inhibitors prescribed, we found that in Brazil, the most frequently-used drug was rivastigmine, at more than 47% of prescriptions. On the other hand, donepezil was the most common drug (greater than 50%)<sup>11</sup> in European countries like Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, and the United Kingdom in 2004, a result similar to that of the United States (66.3%)<sup>15</sup>. The decision for the use of cholinesterase inhibitors, independent of AD severity, should be based on each professional's experience<sup>16</sup> and studies have

still failed to demonstrate greater effectiveness of one drug over the other<sup>17</sup>.

In spite of the notable increase in levels of distribution, the rates of treatment for dementia and AD are still very low. We considered possible factors that have prevented the Brazilian government's goal being reached. First, concerning the differences between the treatment rates of dementia and AD, we highlight that cholinesterase inhibitors, available free of cost in Brazil, are only provided to patients who fulfill the clinical diagnostic criteria established by the Brazilian guidelines for AD and not to patients with other types of dementia<sup>18</sup>. This may have influenced the differences found in the present study between the treatment for dementia syndromes (9.7%) and for AD (16.1%).

Second, not infrequently, the prescription of other drugs for monotherapeutic and/or complementary treatment for AD, as exemplified by Ginkgo Biloba has been observed. *In vitro* studies have shown three biological benefits of this



**Table 3.** Comparison between the use of anticholinesterase drugs in the year 2008 and in the year 2014 in relation to the Brazilian government's goals for treating AD patients (%).

Region/State	2008*	Goal in relation to the AD program (50%)	2014	Goal in relation to the AD program (50%)
Southeast	16.9	33.8	18.4	36.8
São Paulo	22.3	44.6	28.1	56.2
Rio de Janeiro	2.5	5.0	4.0	8.0
Minas Gerais	18.4	36.8	9.5	19.0
Espírito Santo	22.1	44.2	30.9	61.8
Northeast	8.2	16.4	5.8	11.6
Alagoas	7.3	14.6	3.8	7.6
Bahia	4.1	8.2	3.2	6.4
Ceará	14.4	28.8	7.7	15.4
Maranhão	4.7	9.4	4.9	9.8
Paraíba	11.5	23.0	12.3	24.6
Pernambuco	4.0	8.0	4.2	8.4
Piauí	14.4	28.8	6.4	12.8
Rio Grande do Norte	16.7	33.4	9.0	18.0
Sergipe	10.9	21.8	7.7	15.4
Central West	6.0	12.0	7.5	15.0
Distrito Federal	3.6	7.2	2.7	5.4
Goiás	4.1	8.2	7.4	14.8
Mato Grosso	6.4	12.8	4.4	8.8
Mato Grosso do Sul	12.1	24.2	14.6	29.2
North	2.3	4.6	2.6	5.2
Acre	2.8	5.6	4.6	9.2
Amapá	1.2	2.4	0.5	1.0
Amazonas	1.3	2.6	4.5	9.0
Pará	1.8	3.6	1.6	3.2
Rondônia	5.1	10.2	2.6	5.2
Roraima	3.1	6.2	5.3	10.6
Tocantins	4.1	8.2	3.5	7.0
South	8.7	17.4	10.4	20.8
Paraná	13.9	27.8	18.2	36.4
Rio Grande do Sul	1.6	3.2	1.4	2.8
Santa Catarina	15.6	31.2	16.4	32.8
Total	12.0	24.0	16.1	32.2

substance: prevention of neurotoxicity by amyloid beta, the inhibition of apoptotic pathways, and protection from oxidative damage<sup>19</sup>. Nevertheless, previous randomized trials have revealed that long-term use of Ginkgo Biloba extract did not reduce the risk of AD's progression when compared with a placebo<sup>20,21</sup>.

Third, treatment with cholinesterase inhibitors needs periodic reevaluation, every six months, to analyze the drug's effectiveness<sup>18</sup>. If the patient has shown no improvement in, or stagnation of, his or her condition, the medication could be discontinued, as well as if cognition has been severely impaired (very low scores on the Mini-Mental State Examination)<sup>22</sup>. However, longer periods for reevaluation of the cholinesterase inhibitors use may lead the patient to discontinue the treatment or may prevent an increase in its dosage.

Fourth, cholinesterase inhibitors are not free of adverse effects<sup>23</sup>. Intolerance to cholinesterase inhibitors is a relevant

factor for nonadherence to the treatment employed. The most common adverse effects are insomnia, headaches, nausea, vomiting, anorexia, and dyspepsia. Less common are somnolence, dizziness, depression, urinary symptoms, syncope, bradycardia, tremors, and fatigue. Precaution is emphasized for patients with peptic ulcers, a history of convulsions, alterations in cardiac conduction, and asthma<sup>23</sup>.

Fifth, diverse factors may also contribute to under-diagnosis or delay in the diagnosis, which results in the detection of AD only at already-advanced stages. Commonly, the disease's first symptoms are seen by family members as a "natural" manifestation of aging, resulting in delays in consulting a specialist<sup>24</sup>. There may also be a conflict of differential diagnoses, such as depression and B12 hypovitaminosis, the failure of the professional, and/or the lack of resources for diagnostic investigation of probable AD.

Sixth, the international literature emphasizes the relationship between AD and high costs<sup>25</sup>, which could lead to less

medical treatment due to the inability to buy the medication. In Brazil, despite the costs of medications still being high, this is mitigated by free public distribution of medication for all citizens, regardless of their socioeconomic condition<sup>26</sup>.

Seventh, several guidelines have downgraded the evidence status of the cholinesterase inhibitors, indicating their use for moderate to advanced dementia in England and considering their clinical added value as minor in France<sup>14</sup>.

Another important finding of the present study was the clear disparity in the distribution of medications in Brazil, a result that has also been confirmed by other international studies such as one conducted in Australia, which found that geographic isolation and lower socioeconomic conditions were associated with lower rates of prescriptions of cholinesterase inhibitors<sup>27</sup>, and another in the United Kingdom, which found that rates of prescriptions of cholinesterase inhibitors diminished as inequality and financial needs increased<sup>28</sup>.

In the specific case of Brazil, based on analysis by Moraes et al.<sup>10</sup>, and taking into consideration the Program for Supporting Alzheimer's Disease patients' rate of coverage in the year 2008, an increase was noted in the national average of cholinesterase inhibitors distributed by pharmacies dispensing high-cost drugs in 2014, despite some states having a decrease of more than 50%, as in the case of Amapá. It was also observed that this disproportion was maintained among the federative units, facts justified by the socioeconomic inequality that determines access to public health and the minimum quality of infrastructure necessary, as well as the disparity between the number of specialized doctors in each region.

The region with the highest use of cholinesterase inhibitors was the Southeast, followed by the South, the Northeast, the Central West and the North. This is similar to the socioeconomic status of each state considering the gross domestic product, of which the Southeast and the South have highest. This corroborates that the socioeconomic condition is an important determinant for the dispensing of medications. The same results are found if we analyze the number of doctors and specialists. The national rate for specialists/generalists (doctors without specialization) is 1:41. While the South has the highest proportion of specialists in relation to generalists at 2:11, the North has the lowest, at 0:94, which can have an impact on the diagnosis and executing the Program for Supporting Alzheimer's Disease patients<sup>29</sup>. We need to point out that Rio Grande do Sul, the Federal District, and Rio de Janeiro stand out in the difference between the percentages of distribution and their per capita income for 2014. That can be justified by the fact that all Brazilian states have autonomy to determine how medication is dispensed. Some states demand that specific protocols be followed, others demand examinations that are not readily available in the Brazilian public Unified Health System (for, example, magnetic resonance imaging of the brain), and certain states only give the medication to patients treated in certain reference centers<sup>10</sup>.

Other factors could also be responsible for the disparities observed in this study. Some states with poorer socioeconomic conditions tend to have fewer medical specialists trained to prescribe cholinesterase inhibitors and this may impact the AD diagnosis and treatment as reported above. Another problem is that patients who live in smaller cities may travel to other cities in order to obtain the cholinesterase inhibitors<sup>9</sup>. This is a considerable problem in some large states (e.g. North states), in which there are few centers distributing the medications. Some patients may not want to travel several hours to obtain the medication and this could result in under-treatment.

Other possible explanation for this inequality is the administrative processing in supplying cholinesterase inhibitors, since these medications should first be analyzed and approved before being dispensed. A recent study in the State of Minas Gerais (considered a State with high socioeconomic status) showed an average of 39 days for the entire initial administrative process<sup>9</sup>. In other federative states this process could possibly take even longer. Finally, some processes may not be approved for several reasons, such as not fulfilling all inclusion criteria, misdiagnosis, lack of carrying out specific tests (e.g. Mini-Mental State Examination) or incorrect dosage. Therefore, physicians in states with specialized medical centers and universities may be more trained and informed to deal with the administrative processing, which could possibly result in an increased rate of approval of the dispensed drugs.

This study has some limitations that should be taken into consideration. The search for data was done using online government platforms, which can suffer interference because information is manually uploaded and is, therefore, subject to error, making possible an under- or over-notification of information in regard to the distribution of cholinesterase inhibitors by pharmacies dispensing high-cost medications. On the other hand, this data is constantly audited, as it refers to all medications distributed and paid for by the government. Another limitation is the fact that this data does not include commercialization of these medications by the private sector. Even though relatively infrequent in Brazil, this does exist. Finally, the prevalence of dementia and AD has been estimated in accordance with previous surveys by region. It may, therefore, not correspond to the exact proportion of patients with the disease in each region.

The Brazilian government's goal is to reach 50% of those suffering from AD. In the year 2014, Brazil reached 16.1% patients, more than in 2008 and that, despite still being unsatisfactory, indicates growth in Brazil and a potential for improvement in the public program for distributing high-cost medication. Nevertheless, upon taking a more individualized look at the federative units, we recognize significant disparities among some states, principally those in the North that always stand out negatively no matter what criteria are used. Analysis of the data shows the need for major directing of public health measures and access to information for regions with lower indices of distribution.

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